REMARKS

I. Status of the Claims

Claims 1, 10-15, 17-22, 26-28, and 30 are currently pending under examination; whereas claims 2-8 are withdrawn from consideration at this time. Upon entry of the present amendment, claim 1 now recites that the ADNF III polypeptide consists of the amino acid sequence of SEQ ID NO:2. Claims 10, 11, 14 and 15 are canceled. Claims 18-22 are amended to be consistent with the amended base claim(s). No new matter is introduced.

II. Claim Rejections

A. 35 U.S.C. §112, First Paragraph: Written Description

Claims 1, 12, 13, 15, 17-19, and 22 are rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate written description. More specifically, the Examiner asserts that the specification does not provide adequate description for the genus of ADNF polypeptides comprising the active core site of SEQ ID NO:2, because "the genus of ADNF III and ADNF I polypeptides are highly variable in structure" and because the specification "does not provide an adequate description of a sufficient number of structural variants ADNF III and ADNF I polypeptides that function to treat MS" (the last full paragraph on page 3 of the Office Action mailed February 4, 2009). Applicants respectfully traverse the rejection, particularly in view of the present amendment.

As amended, the pending claims are drawn to a method for treating MS by administering a therapeutically effective amount of a pharmaceutical composition comprising an ADNF III polypeptide, which is defined as consisting of the amino acid sequence of SEQ ID NO:2. Because the ADNF polypeptide is now defined by its amino acid sequence, Applicants submit that the written description requirement is met. Accordingly, withdrawal of the written description rejection is respectfully requested.

B. 35 U.S.C. §103

Claims 1, 10, 11, 14, 15, 17, 20-22, 26-28, and 30 are rejected under 35 U.S.C. §103 for alleged obviousness in view of U.S. Patent No. 6,613,740, WO98/35042, and

US2002/0111301. Claims 12, 13, 18, and 19 are rejected for alleged obviousness over U.S. Patent No. 6,613,740, WO98/35042, and US2002/0111301, and further in view of Voet and Goodman. Applicants respectfully traverse the rejections.

To establish a *prima facie* case of obviousness, three basic criteria must be met: first, the prior art references must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to combine the limitations; third, there must be a reasonable expectation of success in combining the limitations. MPEP §2143. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1395-97 (2007) identified several rationales to support a conclusion of obviousness. The key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. §103 should be made explicit.

The pending claims are drawn to a method for treating MS using an ADNF polypeptide that comprises the active core site of SEQ ID NO:2 and reduces disease indications in MOG-induced EAE mice. In contrast, the Examiner has characterized the three main references, U.S. Patent No. 6,613,740, WO98/35042, and US2002/0111301, as teaching the use of an ADNF polypeptide to inhibit neuronal cell death, thereby treating neurological diseases and deficiencies. See pages 6-8 of the Office Action mailed November 27, 2007. The Examiner contends that, because neuronal cell death is a cause of the symptoms of MS, it would have been obvious for a skilled artisan to use the ADNF polypeptide to treat MS. The Examiner further contends that the instantly claimed method is obvious because "[t]here were a finite number of identified, predictable potential solutions to treat related neurological and autoimmune disorders using an ADNF polypeptide or active core sequences thereof." See bottom of page of the Office Action of February 4, 2009. Applicants respectfully disagree with the Examiner.

To begin with, the target condition for treatment in the three cited references is a neurological disease or deficiency caused by neuronal cell death, whereas the target condition for treatment in this application is MS, an autoimmune disorder. These two target conditions have

distinct underlying causes or etiologies. As it is known in the art as well as described in the three cited references, inappropriate or excessive neuronal cell death leads to neurodegenerative conditions including Huntington's disease, AIDS dementia complex, epilepsy, Parkinson's disease, Alzheimer's disease, *etc.* See, *e.g.*, column 6 of U.S. Patent No. 6,613,740. MS, on the other hand, is known as an autoimmune disease in which the patient's own immune cells attack the central nervous system, causing damages to myelin, an insulating substance wrapped around long nerve fibers called axons. Loss of myelin leads to failure of axons to properly transduce electrical signals. Death of neuronal cells in an MS patient is therefore a part of the result or symptom of the pathology, not a cause. In short, the target conditions in the cited references are neurodegeneration, whereas the target condition in this application is neuroinflammation due to autoimmunity, not considered a degenerative disorder among the artisans. The treatment method using the ADNF polypeptide as taught in the cited references and in the instant application thus are applied to two distinct and separate patient populations.

Applicants further submit that, because of the fundamental differences between neurodegeneration and MS, an ordinarily skilled artisan, upon reading the three cited references and learning an ADNF polypeptide's effectiveness in treating neurodegeneration, would not be motivated to use the ADNF polypeptide for treating MS. This is particularly true when considering that neuronal cell death is merely a symptom of MS, but not a cause of the condition. Indeed, as Dr. Gozes attested in her declaration (filed with Applicants' response of September 29, 2008), only until after the surprising discovery by the present inventors that the ADNF polypeptide can inhibit immune cell activity by inhibiting cytokine secretion was it recognized that the polypeptide is useful for treating MS, because of its activity to suppress unwanted immune cell proliferation and therefore reduce or prevent demyelination caused by the immune cells.

The distinct etiologies of neurodegenerative conditions and autoimmune diseases such as MS also preclude a finding of any reasonable expectation of success should an artisan attempt to use an ADNF polypeptide to treat MS. It is well recognized among the medical

professionals that different medical conditions with different underlying causes would likely react differently to the same therapeutic modality.

Also, the Examiner's reasoning is logically flawed in stating that the claimed method of this invention is obvious because there were a finite number of identified, predictable potential solutions to treat related neurological and autoimmune disorders using an ADNF polypeptide. There is in fact no limit in the number of possible ways to treat MS. To illustrate this point, the undersigned attorney performed a quick search at the European Patent Office website for any patent or published application that contains the term "multiple sclerosis" in the title and the terms "multiple sclerosis," "treatment," and "method" in the title or abstract. 142 patent families were identified, none of which relevant to the ADNF polypeptides. This simple search, by no means even close to comprehensive (as evidenced by the fact that it did not identify the present application), demonstrates that there are infinite possibilities in solving the problem of autoimmune disorders such as MS, and these solutions need not at all involve the use of an ADNF polypeptide. The choice of an ADNF polypeptide is therefore not one from an finite number of possibilities.

On the other hand, as discussed above, choosing an ADNF polypeptide as the therapeutic agent to treat MS was not obvious even in view of the available knowledge in the relevant research field at the time this application was filed, because the significant differences between neurodegenerative disorders and autoimmune diseases such as MS negate any motivation and reasonable expectation of success in one's attempt to use an ADNF polypeptide for treating MS. Therefore, there is no predictable result to speak of.

Last but not the least, the experimental data provided in this application show that the ADNF polypeptide consisting of SEQ ID NO:2 is surprisingly effective in inhibiting immune cell proliferation and therefore in providing neuro-protection in the EAE mice. Specifically, the example section beginning on page 30 of the specification describes in detail that the polypeptide of SEQ ID NO:2 significantly improved the clinical conditions of EAE mice (Figure 1 and paragraph 105 on page 31) and significantly suppressed immune cell proliferation upon MOG stimulation at a concentration as high as 25 μg/well (Figure 2 and paragraph 106 on page 31).

This level of effectiveness could not be gleaned from any one of the three cited references. As such, even if the Examiner believes that there exists some basis for one of skill in the art to try an ADNF polypeptide for treating MS in light of the combined teaching of the three cited references, the effectiveness of the ADNF polypeptide of SEQ ID NO:2 actually demonstrated in the EAE mouse experiments and immune cell proliferation assays is nonetheless completely surprising and could not be expected from the cited references. This unexpected quality effectively rebuts any assertion of obviousness. The claimed use of the ADNF polypeptide consisting of SEQ ID NO:2 is therefore not obvious in view of the three cited references.

For these same reasons, the obviousness rejection of claims 12, 13, 18, and 19 should also be withdrawn, because the two additional references, Voet and Goodman, are merely cited to provide additional limitations of the dependent claims (relating to D-amino acids) and do not provide the missing suggestion or reasonable expectation of success.

In summary, no *prima facie* showing of obviousness has been made based on the teaching of U.S. Patent No. 6,613,740, WO98/35042, and US2002/0111301, when considered together in view of the available knowledge in the art at the time of this invention. Moreover, the unexpected effectiveness of the ADNF polypeptide of SEQ ID NO:2 in EAE mouse model experiments and in immune cell proliferation assays as shown in this application rebuts any possible presumption of obviousness. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejections under 35 U.S.C. §103.

C. Double Patenting

Claims 1, 11, 14, 17, 20, and 21 are rejected under the judicially created doctrine of non-statutory double patenting for allegedly being unpatentable over claims 1 and 21 of U.S. Patent No. 7,452,867 (the '867 patent). Claims 1, 10, 11, 14, 15, and 26-28 are provisionally rejected under the judicially created doctrine of non-statutory double patenting for allegedly being unpatentable over claims 56-59 of co-pending U.S. Patent Application No. 11/838,128. Applicants respectfully traverse the rejections.

The MPEP states, a double patenting rejection, if not based on an anticipation theory, is analogous to a failure to meet the nonobviousness requirement under 35 U.S.C. §103. Therefore, the analysis employed in an obviousness-type double patenting parallels the guidelines for a rejection under 35 U.S.C. §103. MPEP §804 II.B.1.

Claims 1 and 21 of the '867 patent recite:

> 1. A method for treating peripheral neurotoxicity in a subject, the method comprising administering a therapeutically effective amount of an ADNF polypeptide to a subject in need thereof, wherein the ADNF polypeptide is a member selected from the group consisting of: (a) an ADNF I polypeptide comprising an active core site having the following amino acid sequence: Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1); (b) an ADNF III polypeptide comprising an active core site having the following amino acid sequence: Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2), and (c) a mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b); wherein said peripheral neurotoxicity is a consequence of treatment with one or more chemical agents.
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> 21. The method of claim 1, wherein said one or more chemical agent is selected from among chemical agents for cancer, multiple sclerosis, gout, arthritis, Behcet's disease, psychiatric disorder, immunosuppression and infectious disease.

The claimed subject matter of these two claims is a method for treating "peripheral neurotoxicity" that is caused by one or more chemical agents, which are used for treating various conditions including multiple sclerosis. The Examiner argues that, because "the symptoms of peripheral neurotoxicity are commensurate with the symptoms of MS and that a treatment for peripheral neurotoxicity may be affected by treatment with a chemical agent that treats MS," treatment of peripheral neurotoxicity by an ADNF polypeptide renders it obvious to use of the ADNF polypeptide for treating multiple sclerosis. Applicants cannot agree with this reasoning.

First of all, similar symptoms are often observed among various distinct medical conditions, yet these conditions are not likely to be treated with the same therapeutic agent, because a physician would recognize the different underlying etiologies for the conditions. For

instance, a patient running a high fever could be suffering from a broad range of medical conditions with very different underlying causes. A physician certainly would not treat a patient suffering from a viral infection the same way as he would treat another patient suffering from a bacterial infection. The Examiner has not provided any logical basis for the assertion that, because peripheral neurotoxicity has certain symptoms similar to those of MS, it would be obvious for a person of skill in the art to consider using a therapeutic agent effective for treating peripheral neurotoxicity to treat MS.

Second, the requisite reasonable expectation of success cannot be established either. Even assuming, for the sake of argument, that an artisan would somehow become motivated to try using a therapeutic agent that is indicated by the '867 patent as effective for treating peripheral neurotoxicity, such as the ADNF polypeptide having the amino acid sequence of SEQ ID NO:2, to treat MS, it simply could not be expected (until the present inventors showed that the ADNF polypeptide is indeed capable of providing protective effect in EAE mouse model) that such agent would indeed be effective for the treatment of MS as well. This is again due to the fact that peripheral neurotoxicity and MS have distinct etiologies, which to a large extent determine the effectiveness of a medication.

As such, there is neither any motivation to use an ADNF polypeptide having the amino acid sequence of SEQ ID NO:2 for treating MS nor any reasonable expectation that the ADNF polypeptide would be effective for treating MS. The obviousness-type double patenting rejection based on the claims of the '867 patent is therefore unfounded and should be properly withdrawn.

With regard to the provisional double patenting rejection over USSN 11/838,128, Applicant submit that, once all other rejections are overcome, the Examiner should withdraw the provisional double patenting rejection and allow the claims pending in the present application. According to the MPEP §804 I.B.1, if the provisional obviousness-type double patenting rejection in two applications are the only rejection remaining in those applications, the examiner should withdraw the double patenting rejection in the earlier filed the application and permit the application to issue as a patent without the need of a terminal disclaimer. This appears to be the

situation in the present case, as the instant application was filed December 29, 2003, earlier than the filing date of USSN 11/838,128, August 13, 2007.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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